RespireRx Pharmaceuticals Inc. Announces Publication of a Manuscript Describing Its Newest Neuromodulator for Pharmacoresistant Epilepsy and Chronic Pain

Glen Rock, N.J., January 24, 2022 /Globe Newswire – RespireRx Pharmaceuticals Inc. (OTCQ:RSPI) ("RespireRx" or the "Company"), a leader in the discovery and development of innovative and revolutionary treatments to combat diseases caused by disruption of neuronal signaling, is pleased to announce that scientists associated with the Company have published a manuscript detailing the pharmacology of its newest asset, KRM-II81. The paper titled "The imidazodiazepine, KRM-II-81: An example of a newly emerging generation of GABAkines for neurological and psychiatric disorders" was published in the peer reviewed journal *Pharmacology Biochemistry and Behavior* (Elsevier, https://authors.elsevier.com/sd/article/S0091-3057(21)00220-3).

The multidisciplinary team of authors was led by Drs. Rok Cerne and Jeffrey M. Witkin, scientists at RespireRx with contributions from academic collaborators at the University of Wisconsin-Milwaukee, Ascension St. Vincent and Indiana University/Purdue University, and the Victoria University of Wellington in New Zealand. Authors also include Arnold Lippa, RespireRx Executive Chairman and Chief Scientific Officer. Dr. Lippa is a pioneer in this field since its inception being the first to identify compounds with anxiolytic effects without sedation and to bring them into clinical development (e.g., ocinaplon) while another co-author, Dr. James M. Cook has been inventing key compounds for modulation of GABA-A receptors for several decades.

The article emphasizes several important points. First, a drought in the pharmaceutical pipeline for medicines that enhance the inhibitory neurotransmitter, GABA (GABAkines), has been broken. The excitement in the field was heralded by the FDA approval of brexanolone for severe post-partum depression in 2019 and has flooded the developmental pipeline with at least 10 new compounds at various stages of development. Excitement in the pharmaceutical, medical, and patient communities is supported by the historical blockbuster nature of drugs with this mechanism of action (e.g., Valium and Xanax). Secondly, the pharmacological profile of the preclinical compound KRM-II-81 is highlighted given the extensive and robust data package surrounding this asset. KRM-II-81, originally synthesized by Dr. Cook, is being developed by the Company's EndeavourRx business unit because of its ability to selectively amplify inhibitory neurotransmission at a highly specific, subset of GABA-A receptors, thus producing a unique efficacy profile with reduced side effects. The Company currently is focusing on developing KRM-II-81 for the treatment of epilepsy and pain.

KRM-II-81 has a preclinical profile predicting efficacy against pharmacoresistant epilepsies, traumatic brain injury, and neuropathic pain. Other key features of the pharmacology of this compound are its low sedation rate, lack of tolerance development, and the ability to hold seizure development in check. Given the huge unmet medical need in these areas, the advent of such a compound is significant. It is argued in the manuscript, that the ability to effectively move compounds of this mechanism along the developmental pipeline today requires the steadfast and devoted work of biotech companies fully committed to the enterprise. In the area of epilepsy, data are highlighted to support the greater efficacy of KRM-II-81 over that of standard-of-care antiepileptic compounds in models predictive of treating epilepsies that are resistant to available medicines. Also, with the lack of specifically approved medicines for post-traumatic epilepsy, the ability of KRM-II-81 to suppress cortical hyperactivity after traumatic brain injury suggests a potential path forward. In support of its potential clinical efficacy, translational studies have demonstrated the ability

of KRM-II-81 to dramatically reduce epileptiform electrical activity when administered *in situ* to tissue removed from the brains of treatment resistant epileptic patients undergoing surgery by co-author Jodi L. Smith, who heads the Laboratory of Antiepileptic Drug Discovery at Ascension St. Vincent in Indianapolis, Indiana. The data in animal models of chronic pain are equally impressive where the findings from multiple studies confirm the robust activity of KRM-II-81 without development of tolerance, a serious health and societal issue for opioid pain therapies. It is also argued by the data that the ability of KRM-II-81 to produce anti-anxiety and antidepressant-like actions bodes well for its potential use to ameliorate these comorbid symptoms of epilepsy and pain.

Senior author Dr. Witkin commented, "A pharmacological profile like that of KRM-II-81 immediately suggests a potential novel and improved therapeutic agent. At a time when GABAkines are again being enthusiastically developed, we are proud to be a part of the science devoted to improving the care of patients in need." Dr. Lippa added, "We are very excited about developing KRM-II-81 and going forward into IND enabling studies. Pending clinical validation, we believe that KRM-II-81 has the potential to represent a breakthrough treatment for epilepsy as well as the long sought-after alternative to narcotic analgesics for chronic pain."

About RespireRx Pharmaceuticals Inc.

RespireRx Pharmaceuticals Inc. is a leader in the discovery and development of medicines for the treatment of psychiatric and neurological disorders, with a focus on treatment options that address conditions affecting millions of people, but for which there are few or poor treatment options, including obstructive sleep apnea ("OSA"), attention deficit hyperactivity disorder ("ADHD"), epilepsy, chronic pain and recovery from spinal cord injury ("SCI"), as well as certain neurological orphan diseases. RespireRx is developing a pipeline of new and re-purposed drug products based on our broad patent portfolios for two drug platforms: (i) pharmaceutical cannabinoids, which include dronabinol, a synthetic form of Δ9-tetrahydrocannabinol ("Δ9-THC") that acts upon the nervous system's endogenous cannabinoid receptors and (ii) neuromodulators, which include AMPAkines and GABAkines, proprietary chemical entities that positively modulate (positive allosteric modulators or "PAMs") AMPA-type glutamate receptors and $GABA_A$ receptors, respectively.

The Company holds exclusive licenses and owns patents and patent applications or rights thereto for certain families of chemical compounds that claim the chemical structures and their uses in the treatment of a variety of disorders, as well as claims for novel uses of known drugs.

***ResolutionRx: Pharmaceutical Cannabinoids*.**

Dronabinol. RespireRx is developing dronabinol, Δ-9-THC, a synthetic version of the naturally occurring substance in the cannabis plant, for the treatment of OSA, a serious respiratory disorder that impacts an estimated 29.4 million people in the United States according to the American Academy of Sleep Medicine ("AASM"), published in August 2016. OSA has been linked to increased risk for hypertension, heart failure, depression, and diabetes, and has an annual economic cost in the United States of $162 billion according to the AASM. There are no approved drug treatments for OSA.

Two Phase 2 clinical trials have been completed demonstrating the ability of dronabinol to significantly reduce the symptoms of OSA and, subject to raising sufficient financing (of which no assurance can be provided) and pending the outcome of an intended meeting with the FDA, RespireRx believes that it will be able to commence a pharmacokinetic study for a recently discovered and to-be-developed formulation followed by a Phase 3 clinical study for the treatment of OSA with the new formulation. Because dronabinol is already FDA approved for the treatment of AIDS related anorexia and chemotherapy induced nausea and vomiting, the Company further believes that its re-purposing strategy would only require approval by the FDA of a 505(b)(2) new drug application ("NDA"), an efficient regulatory pathway that allows the use of publicly available data.

EndeavourRx: Neuromodulators

GABAkines. Under a License Agreement with the University of Wisconsin-Milwaukee Research Foundation, Inc. ("UWMRF"), RespireRx has licensed rights to certain selectively acting GABAkines because of their ability to selectively amplify inhibitory neurotransmission at a highly specific, subset of $GABA_A$ receptors, thus producing a unique efficacy profile with reduced side effects. Preclinical studies have documented their efficacy in a broad array of animal models of interrelated neurological and psychiatric disorders including epilepsy, pain, anxiety, and depression in the absence of or with greatly reduced propensity to produce sedation, motor-impairment, tolerance, dependence and abuse. The Company currently is focusing on developing KRM-II-81 for the treatment of epilepsy and pain.

KRM-II-81 has displayed a high degree of anti-convulsant activity in a broad range of preclinical studies, including in treatment resistant and pharmaco-resistant models. Not only was KRM-II-81 highly effective in these models, but pharmaco-resistance or tolerance did not develop to its anti-convulsant properties. These latter results are particularly important because pharmaco-resistance occurs when medications that once controlled seizures lose efficacy as a result of chronic use and it is a principal reason some epileptic patients require brain surgery to control their seizures. In support of its potential clinical efficacy, translational studies have demonstrated the ability of KRM-II-81 to dramatically reduce epileptiform electrical activity when administered *in situ* to brain slices excised from treatment resistant epileptic patients undergoing surgery.

In addition, KRM-II-81 has displayed a high degree of analgesic activity in a broad range of preclinical studies. In intact animal models of acute and chronic pain, the analgesic efficacy of KRM-II-81 was comparable to or greater than commonly used analgesics. At the same time, KRM-II-81 did not display side effects such as sedation and motor impairment, but even more importantly, it did not produce tolerance, dependence, respiratory depression or behavioral changes indicative of abuse liability, which are produced by opioid narcotics and are at the heart of the opioid epidemic.

AMPAkines. Through an extensive translational research effort from the cellular level through Phase 2 clinical trials, the Company has developed a family of novel, low impact AMPAkines, including CX717, CX1739 and CX1942 that may have clinical application in the treatment of CNS-driven neurobehavioral and cognitive disorders, spinal cord injury, neurological diseases, and certain orphan indications. Our lead clinical compounds, CX717 and CX1739, have successfully completed multiple Phase 1 safety trials. Both compounds have also completed Phase 2 proof of concept trials demonstrating target engagement, by antagonizing the ability of opioids to induce respiratory depression.

AMPAkines have demonstrated positive activity in animal models of ADHD, results that have been extended translationally into statistically significant improvement of symptoms observed in a Phase 2 human clinical trial of CX717 in adults with ADHD. Statistically significant therapeutic effects were observed within one week. We believe AMPAkines may represent a novel, non-stimulant treatment for ADHD with a more rapid onset of action than alternative non stimulants, such as Straterra® (atomoxetine), and without the drawbacks of amphetamine-type stimulants.

In a series of important studies funded by grants from the National Institutes of Health and published in a number of peer reviewed articles, Dr. David Fuller (University of Florida), a long-time RespireRx collaborator, has demonstrated the ability of CX1739 and CX717, the Company's lead AMPAkines, to improve motor nerve activity and muscle function in animal models of spinal cord injury (SCI).

Additional information about RespireRx and the matters discussed herein can be obtained on the Company's web-site at www.RespireRx.com or in the Company's filings with the Securities and Exchange Commission at www.sec.gov.

Not a Securities Offering or Solicitation

This communication shall not constitute an offer to sell or the solicitation of an offer to buy any securities, nor shall there be any sales of securities in any jurisdiction in which such offer, solicitation or sale of securities would be unlawful before registration or qualification under the laws of such jurisdiction.

Cautionary Note Regarding Forward-Looking Statements

This press release contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act") and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and the Company intends that such forward-looking statements be subject to the safe harbor created thereby. These might include statements regarding the Company's future plans, targets, estimates, assumptions, financial position, business strategy and other plans and objectives for future operations, and assumptions and predictions about research and development efforts, including, but not limited to, preclinical and clinical research design, execution, timing, costs and results, future product demand, supply, manufacturing, costs, marketing and pricing factors.

In some cases, forward-looking statements may be identified by words including "assumes," "could," "ongoing," "potential," "predicts," "projects," "should," "will," "would," "anticipates," "believes," "intends," "estimates," "expects," "plans," "contemplates," "targets," "continues," "budgets," "may," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words, and such statements may include, but are not limited to, statements regarding (i) future research plans, expenditures and results, (ii) potential collaborative arrangements, (iii) the potential utility of the Company's products candidates, (iv) reorganization plans, and (v) the need for, and availability of, additional financing. Forward-looking statements are based on information available at the time the statements are made and involve known and unknown risks, uncertainties and other factors that may cause our results, levels of activity, performance or achievements to be materially different from the information expressed or implied by the forward-looking statements in this press release.

These factors include but are not limited to, regulatory policies or changes thereto, available cash, research and development results, issuance of patents, competition from other similar businesses, interest of third parties in collaborations with us, and market and general economic factors, and other risk factors disclosed in "Item 1A. Risk Factors" in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2020, as filed with the SEC on April 15, 2021 (the "2020 Form 10-K").

You should read these risk factors and the other cautionary statements made in the Company's filings as being applicable to all related forward-looking statements wherever they appear in this press release. We cannot assure you that the forward-looking statements in this press release will prove to be accurate and therefore prospective investors, as well as potential collaborators and other potential stakeholders, are encouraged not to place undue reliance on forward-looking statements. You should read this press release completely. Other than as required by law, we undertake no obligation to update or revise these forward-looking statements, even though our situation may change in the future.

We caution investors, as well as potential collaborators and other potential stakeholders, not to place undue reliance on any forward-looking statement that speaks only as of the date made and to recognize that forward-looking statements are predictions of future results, which may not occur as anticipated. Actual results could differ materially from those anticipated in the forward-looking statements and from historical results, due to the risks and uncertainties described in the 2020 Form 10-K and in this press release, as well as others that we may consider immaterial or do not anticipate at this time. These forward-looking statements are based on assumptions regarding the Company's business and technology, which involve judgments with respect to, among other things,

future scientific, economic, regulatory and competitive conditions, collaborations with third parties, and future business decisions, all of which are difficult or impossible to predict accurately and many of which are beyond the Company's control. Although we believe that the expectations reflected in our forward-looking statements are reasonable, we do not know whether our expectations will prove correct. Our expectations reflected in our forward-looking statements can be affected by inaccurate assumptions that we might make or by known or unknown risks and uncertainties, including those described in the 2020 Form 10-K and in this press release. These risks and uncertainties are not exclusive and further information concerning us and our business, including factors that potentially could materially affect our financial results or condition, may emerge from time to time.

For more information about the risks and uncertainties the Company faces, see "Item 1A. Risk Factors" in our 2020 Form 10-K. Forward-looking statements speak only as of the date they are made. The Company does not undertake and specifically declines any obligation to update any forward-looking statements or to publicly announce the results of any revisions to any statements to reflect new information or future events or developments. We advise investors, as well as potential collaborators and other potential stakeholders, to consult any further disclosures we may make on related subjects in our annual reports on Form 10-K and other reports that we file with or furnish to the SEC.

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